東京大学 THE UNIVERSITY OF TOKYO

臺北醫學大學 TAIPEI MEDICAL UNIVERSITY

2015 02.10 (二) 09:00

The University of Tokyo-Taipei Medical University Joint Symposium

Venue: 4F Conference Hall,
The United Medical Building (Front Building)
Taipei Medical University, Taipei, Taiwan

東京大學與臺北醫學大學學術合作研討會

{受邀講者}

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賴鴻政	教授	臺北醫學大學
黃彥華	教授	臺北醫學大學
林琬琬	教授	臺北醫學大學
張偉嶠	副教授	臺北醫學大學
邱馨慧	助理教授	臺北醫學大學
鄭雅文	教授	臺北醫學大學

(按演講順序排列)

主辦單位：臺北醫學大學醫學院
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The University of Tokyo - Taipei Medical University Joint Symposium

東京大学と台北医学大学
学術合同研究会

東京大學與臺北醫學大學
學術合作研討會

Feb. 10, 2015

Taipei Medical University

Taipei, Taiwan

Welcome Letter

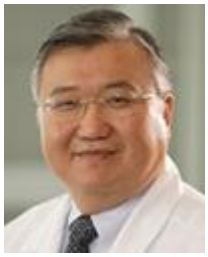
Dear colleagues and friends,

On behalf of Taipei Medical University, we are delighted to welcome you to participate in the coming conference of "2015 The University of Tokyo- Taipei Medical University (UT-TMU) Joint Symposium" which will be held on February 10th, 2015 at Taipei Medical University, Taipei, Taiwan. The conference will be a forum to promote academic communication and research collaborations between scientists who are interested in cancer research and biomedicine in the University of Tokyo and Taipei Medical University.

I would like to express my sincere thanks to Dean Prof. Kohei Miyazono of The University of Tokyo, the most outstanding scientist working on TGF-β and cancer research, to being our keynote speaker. We also invited 7 outstanding speakers from Taipei Medical University to share with us their recent progress in cancer medicine, including TGF-β, connective tissue growth factor and fibrocyte differentiation, epigenetic regulation, cancer stemness, energy homeostasis and mitochondrial signals, calcium channel, and virus infection. I hope the UT-TMU Joint symposium would represent you a lifetime opportunity to meet up the distinguished guest and to participate an international based and in-depth discussions in Taiwan. We believe that the symposium presentations will inspire fruitful results for all participants. We hope your experience at this conference will be valuable and memorable.

Thank you again for your participation, and we look forward to seeing you in Taipei Medical University.

Yours sincerely,



Yun Yen M.D., Ph. D., F.A.C.P.
President and Distinguished Professor
Taipei Medical University
Taipei, Taiwan

Table of content

Taipei Medical University (TMU)

Taipei Medical University (TMU), formerly known as Taipei Medical College (TMC), was founded on June 1, 1960 by Dr. Shui-Wang Hu, Dr. Cheng-Tien Hsu and other medical professionals and devoted educators. TMU is located on Wuxing Street in eastern Taipei.

Most of more than 30,000 TMU graduates serve in medical institutions and clinics, while many others are prominent figures in the fields of research, politics, and business. TMU has 7 colleges, 12 undergraduate schools and 14 graduate institutes as well as three affiliated hospitals - TMU Hospital, Wan Fang Hospital, and Shuangho Hospital. With approximately 3,000 beds, TMU is one of the largest health care systems and offers top-quality teaching, research and clinical services in the Taipei metropolitan area. We work continuously to improve the quality of teaching, research and clinical services with the goal of becoming a fully internationalized university that ranks in the top tier worldwide.

Taipei Medical University Hospital

Taipei Medical University Hospital (TMUH) has been serving Taipei for thirty years. Conveniently located near Taiwan's landmark Taipei 101 tower, TMUH offers a warm atmosphere and friendly environment as well as world-tier medical equipment, top-quality medical personnel and patient-centered service. The mission of TMUH encompasses education, research and service through innovation, excellence and commitment to life.

We provide our international friends the same high-quality, efficient and accessible medical services. Our steps toward becoming an internationalized medical center include overseas emergency medical transportation, educational exchanges and medical missions. In addition, we help expatriates in Taiwan with quick and convenient medical services and provide assistance for overseas medical activities, collaborating with the government in expanding medical diplomacy as well as setting up a global network of medical contacts.

Taipei Medical University Wan Fang Hospital

Wan Fang Medical Center dedicated to serving the surrounding area, and is committed to community health promotion. Built in 1989, the Wan-Fang Hospital is the first hospital owned by Taipei City government while run by civilians. In 1998, it passed the Regional Hospital Accreditation and was awarded the international quality certificate of ISO-9002. In 2006, it was awarded the Joint Commission International (JCI) Accreditation. It is the Affiliate Hospital of Taipei Medical University and includes 42 integrated departments of medicine.

Taipei Medical University Shuang Ho Hospital

Shuang Ho Hospital opened on July 1, 2008, with 1580 beds. It is the largest hospital in Taipei County, but also forms a medical “golden triangle” with the Taipei Medical University Hospital and Wan Fang Medical Center, giving a total capacity of over 3000 beds.

Shuang Ho Hospital focuses on providing emergency and critical care, as it is responsible for first response for Taipei County as the only hospital with a medical helicopter and landing pad. Shuang Ho also has the largest dentistry department, with general and family dentistry and six additional specialized clinics. The hospital has the nation's first disabled patient oral health care center to serve the more than 130,000 disabled people in Taipei County. The Kidney Dialysis Center's method of isolating beds, equipment and sections leads the nation in reducing hepatitis C infection. The hospital plans further expansion in the areas of cancer treatment, neurology, minimally invasive surgery, optometry and vision science, health management, cardiology, rehabilitation, trauma surgery and international medical care.

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劉高輝 Kao-Hui Liu

温恒京 Heng-Ching Wen

邱意庭 Yi-Ting Chiu

協辦單位

秘書處、教務處、研究發展處、學務處、總務處、資訊處、國際事務處、圖書館

Schedule at a Glance

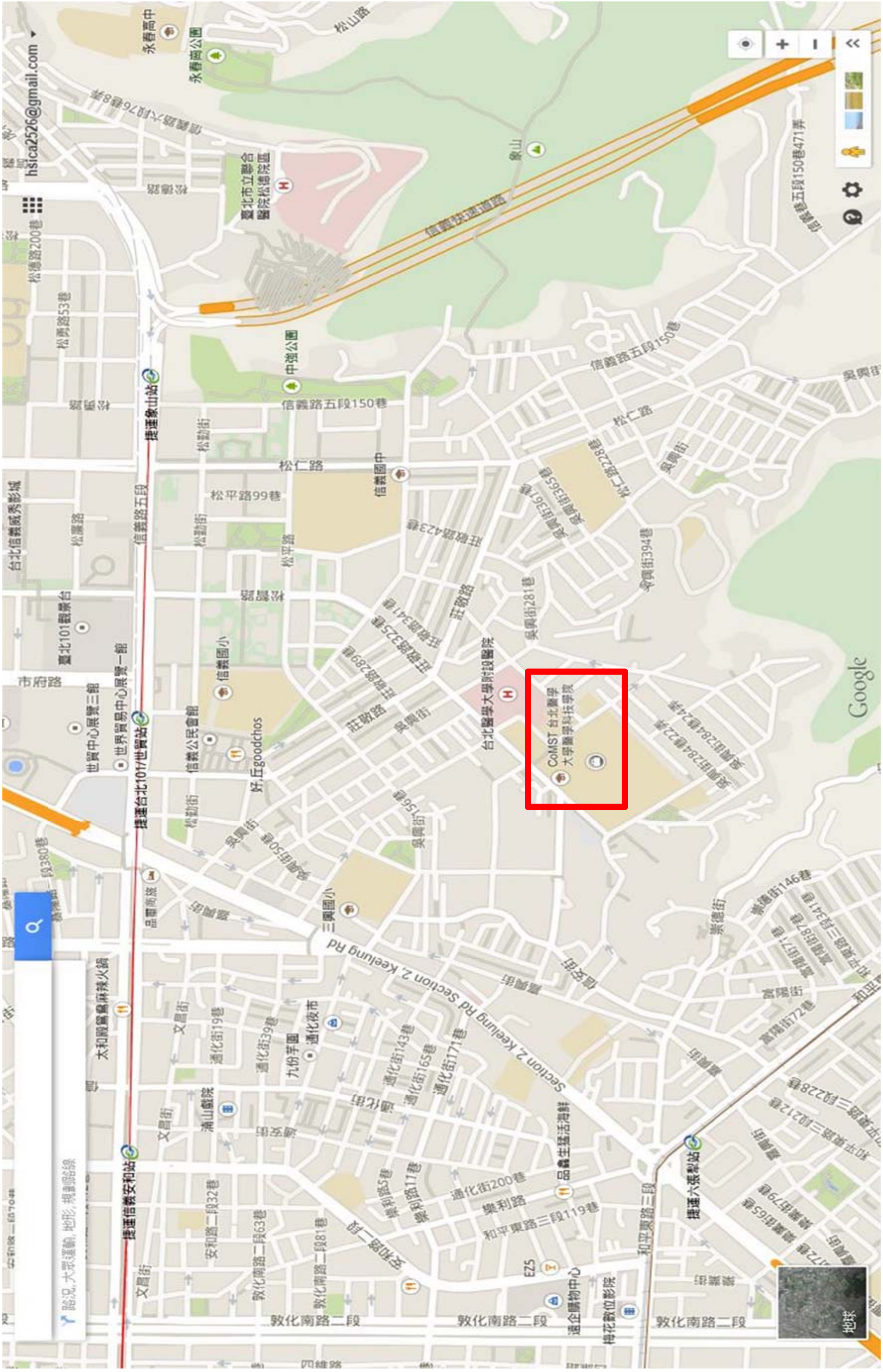
2015 The University of Tokyo - Taipei Medical University Joint Symposium

Master of Ceremony: Liang-Tzung Lin, Ph.D. (林良宗助理教授)
Venue: 4F Conference Hall, The United Medical Building (Front Building), Taipei Medical University, Taipei, Taiwan

2015/ 2/ 10 (Tue.)	
09:10~09:20	**Opening Remarks** **Yun Yen, M.D., Ph.D., F.A.C.P. (閻雲校長)** *President and Distinguished Professor, Taipei Medical University, Taipei, Taiwan* **Chao-Ching Huang, M.D. (黃朝慶院長)** *Professor and Dean, College of Medicine, Taipei Medical University, Taipei, Taiwan*
09:20~09:30	**UT-TMU MOU Exchange Ceremony**
09:30~10:30	**Moderator: Chao-Ching Huang, M.D. (黃朝慶院長)** *Professor and Dean, College of Medicine, Taipei Medical University, Taipei, Taiwan* **Keynote Speaker:** **Kohei Miyazono, M.D. Ph.D. (宮園浩平院長)** **TGF-β Signaling in Regulation of Cancer** *Professor and Dean, Department of Molecular Pathology, Graduate School of Medicine, The University of Tokyo, Tokyo, Japan*
10:30~10:50	**Group Photography and Coffee Break**
10:50~11:15	**Moderator: Jacqueline Whang-Peng, M.D. (彭汪嘉康院士)** *Superintendent, Taipei Cancer Center, Taipei Medical University, Taipei, Taiwan* *Academician, Academia Sinica, Taiwan* *Professor, College of Medicine Science and Technology, Taipei Medical University, Taipei, Taiwan* **Speaker: Chien-Huang Lin, Ph.D. (林建煌副校長)** **Connective Tissue Growth Factor(CTGF) Mediates Fibrocyte Differentiation in Chronic Obstructive Asthma** *Vice President, Taipei Medical University, Taipei, Taiwan* *Professor , Graduate Institute of Medical Sciences, College of Medicine, Taipei Medical University, Taipei, Taiwan*
11:15~11:40	**Speaker: Hung-Cheng Lai, M.D., Ph.D. (賴鴻政副院長)** **DNA Methylation Development of Biomarkers in GYN Cancers: Translating Research to Clinical Practice** *Vice Superintendent, Shuang Ho Hospital Ministry of Health and Welfare, Taipei, Taiwan* *Professor, Department of Obstetrics and Gynecology, School of Medicine, College of Medicine, Taipei Medical University, Taipei, Taiwan*
11:40~12:05	**Speaker: Rita Yen-Hua Huang, Ph.D. (黃彥華主任)** **Homeostasis of Pluripotent Transcription Factor OCT4 in Stem Cells and Cancer** *Professor and Director, Department of Biochemistry and Molecular Cell Biology, College of Medicine, Taipei Medical University, Taipei, Taiwan*

12:20~14:20	**Lunch**
	Moderator: Ho Yuan-Soon, Ph.D. (何元順所長) *Distinguished Professor, Taipei Medical University, Taipei, Taiwan* *Professor and Director, Graduate Institute of Medical Sciences, College of Medicine, Taipei Medical University, Taipei, Taiwan* *Professor, School of Medical Laboratory Science and Biotechnology, Taipei Medical University, Taipei, Taiwan*
14:20~14:45	**Speaker: Wan-Wan Lin, Ph.D. (林琬琬所長)** **Energy Homeostasis and Mitochondrial Signals in Cancer Cells under Nutrient Starvation** *Professor and Director, Department of Pharmacology, National Taiwan University, Taipei, Taiwan* *Professor, Graduate Institute of Medical Sciences, College of Medicine, Taipei Medical University, Taipei, Taiwan*
14:45~15:10	**Speaker: Wei-Chiao Chang, Ph.D. (張偉嶠主任)** **Store-operated Calcium Channel and Human Diseases** *Associate Professor and Director, Master Program for Clinical Pharmacogenomics and Pharmacoproteomics, College of Pharmacy, Taipei Medical University, Taipei, Taiwan*
15:10~15:35	**Speaker: Hsin-Hui Chiu, M.D. , Ph.D. (邱馨慧助理教授)** **TGF beta and Angiotensin Networking in Vascular Remodeling and Potential Ttherapeutic Targets in Marfan Syndrome** *Assistant Professor, Department of Pediatrics , College of Medicine, Taipei Medical University, Taipei, Taiwan,*
14:35~16:00	**Speaker: Ya-Wen Cheng, Ph.D. (鄭雅文主任)** **Role of HPV in Lung Cancer: Pathogenesis and Therapeutic Effect** *Professor and Director, The Ph. D. Program for Cancer Biology and Drug Discovery, College of Medical Sciences and Technology, Taipei Medical University, Taipei, Taiwan*
16:00~16:20	**Closing Remark** **Chao-Ching Huang, M.D. (黃朝慶院長)** *Professor and Dean, College of Medicine, Taipei Medical University, Taipei, Taiwan*

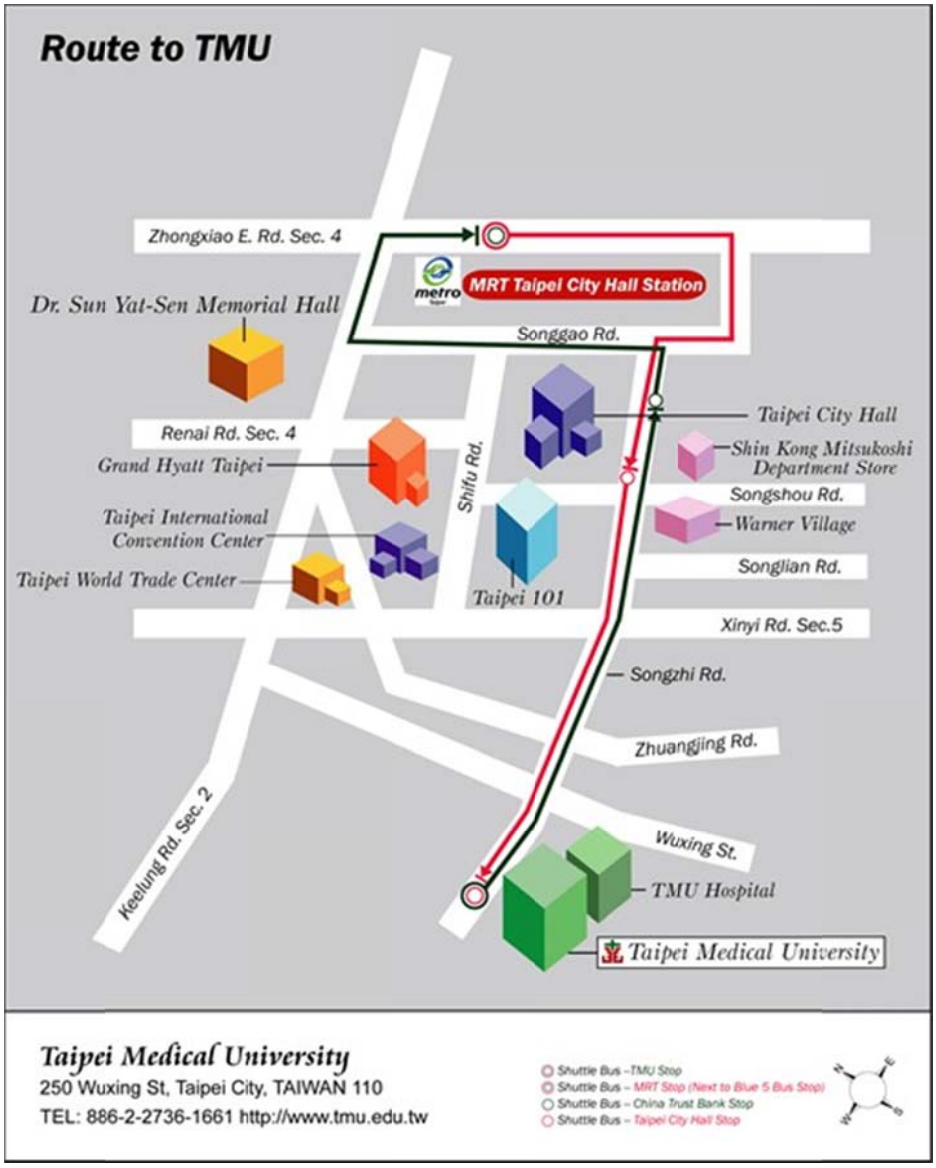
Local Map


hsica2526@gmail.com
永春高中
永春公園
松山路
象山
信義快速道路
臺北市立聯合醫院松德院區
中強公園
信義路五段150巷
捷運象山站
信義路五段
松仁路
信義國中
松平路99巷
臺北101觀景台
市府路
世貿中心展覽三館
世界貿易中心展覽一館
捷運台北101/世貿站
信義國小
信義公民會館
莊敬路
吳興街
台北醫學大學附設醫院
CoMST 台北醫學大學醫學科技學院
三興國小
Section 2, Keelung Rd
通化夜市
捷運信義安和站
和平東路三段
敦化南路二段
捷運六張犁站
Google

Transportation

TMU shuttle service

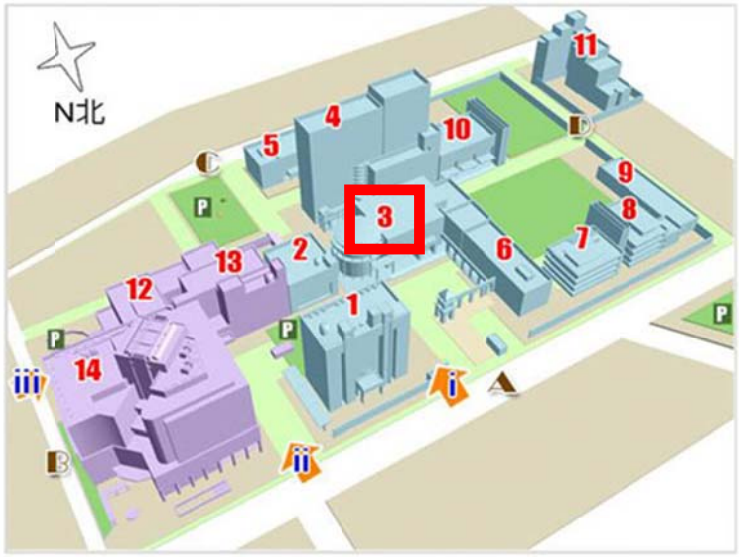
The school is located near MRT Taipei City Hall (Blue Line) and Liuzhangli (Brown Line) stations, and TMU provides shuttle services to both. Buses run every 15 minutes between the City Hall station and TMU (see route map), while the Liuzhangli shuttle bus runs every half an hour.



Public transit

Public transportation to TMU includes bus lines 266, 288, 226, 1, 235, 22, 33 and Blue 5.

Map Guidance



Roads & Streets

A. 220 Lane,WuXing Street
B. Wusing Street(WuXing Street)
C. 284 Lane,WuXing Street
D. 22 Alley,284 Lane,WuXing Street

Entrances

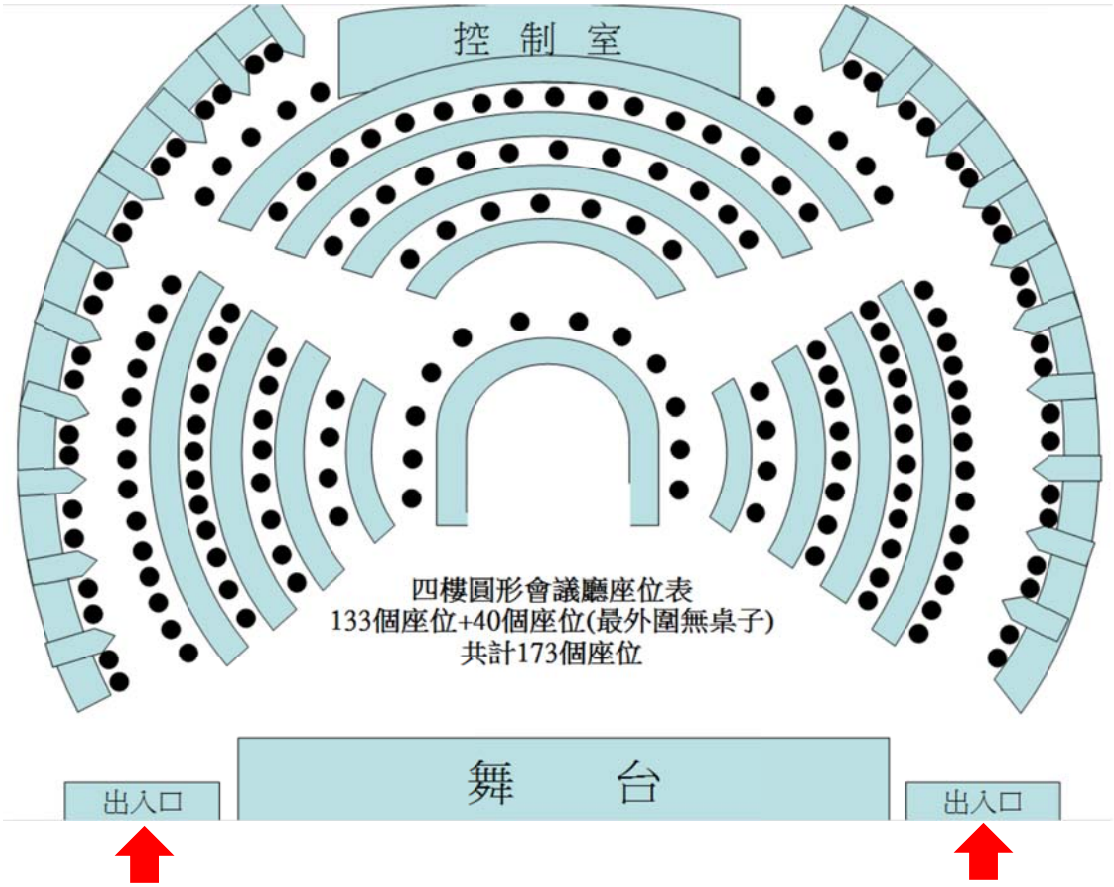
i. University Entrance
ii. Hospital Entrance
iii. Ambulance Entrance

Buildings

1. Health Science Building
2. Auditorium
3. United Medical Building (Front Building)
4. United Medical Building (Back Building)
5. Oral Medicine Building
6. Instruction Building
7. Medical Laboratory Science and Biotechnology Building A
8. Medical Laboratory Science and Biotechnology Building B
9. Morphology Building
10. Gymnasium
11. Mushan Dormitory
12. First Building, Taipei Medical University Hospital
13. Second Building, Taipei Medical University Hospital
14. Third Building, Taipei Medical University Hospital

Floor Plan

The United Medical Front Building, 4th Floor.

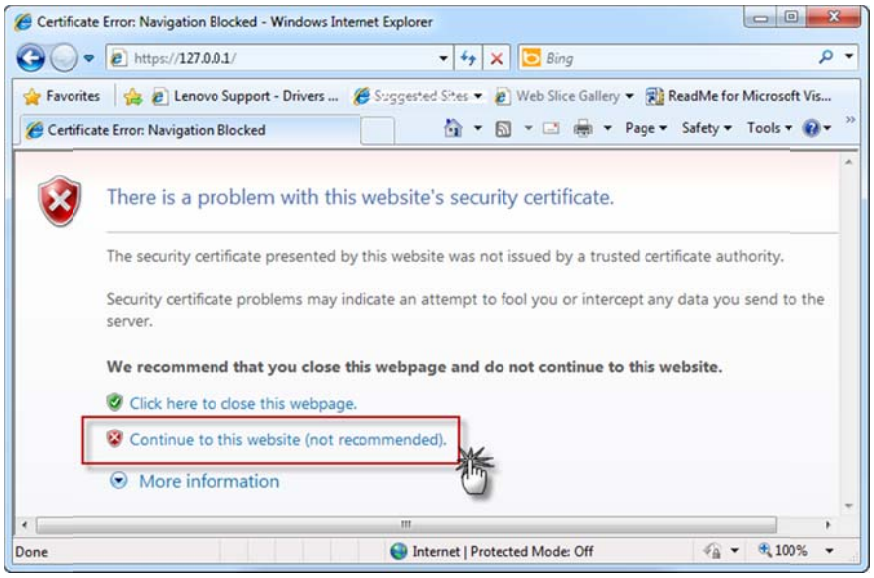


Wireless Setting

◎ On campus SSID:
TMU-WLAN
TMU-wireless

◎ Users from other Universities of Taiwan:
Username: your school email (include "@XXX.edu.tw")
Password: as your school email's password

◎ Other Users:
Username: utokyo01 Password: bhz211au
Username: utokyo02 Password: yqh329jm
Username: utokyo03 Password: svn669bh



Session I

Moderator:

Chao-Ching Huang, M.D.
(黃朝慶院長)

Professor and Dean,
College of Medicine,
Taipei Medical University, Taipei, Taiwan

Distinguished Professor,
Department of Pediatrics, College of Medicine, National Cheng Kung University, Tainan, Taiwan

Adjunct Professor, Department of Pediatrics,
College of Medicine,
National Taiwan University, Taipei, Taiwan

Attending Physician & Pediatric Neurologist,
Department of Pediatrics,
Wan-Fang Hospital and Taipei Medical University Hospital, Taipei Medical University, Taipei, Taiwan

President,
Children's Epilepsy Association of Taiwan, Taipei, Taiwan

Kohei Miyazono, M.D. Ph. D. (宮園浩平院長)

Professor and Chair,
Department of Molecular Pathology, Graduate School of Medicine, The University of Tokyo, Japan

Dean,
Graduate School of Medicine, The University of Tokyo, Japan

Guest Professor,
Ludwig Institute for Cancer Research, University of Uppsala, Uppsala, Sweden

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Recent Selected Publications:

Original Research articles (selected from over 330 articles)

◎ **Miyazono K,** Hellman U, Wernstedt C, and Heldin C-H. (1988) Latent high molecular weight complex of transforming growth factor β1: Purification from human platelets and structural characterization. ***J Biol Chem***. 263, 6407-6415.

◎ Franzén P, ten Dijke P, Ichijo H, Yamashita H, Schulz P, Heldin C-H, and **Miyazono K.** (1993) Cloning of a TGFβ type I receptor that forms a heteromeric complex with the TGFβ type II receptor. ***Cell.*** 75, 681-692.

◎ ten Dijke P, Yamashita H, Ichijo H, Franzén P, Laiho M, **Miyazono K**, and Heldin C-H. (1994) Characterization of type I receptors for transfoming growth factor-β and activin. ***Science.*** 264, 101-104.

◎ ten Dijke P, Yamashita H, Sampath TK, Reddi AH, Estevez M, Riddle DL, Ichijo H, Heldin C-H, and **Miyazono K**. (1994) Identification of type I receptors for osteogenic protein-1 and bone morphogenetic protein-4. ***J Biol Chem.*** 269, 16985-16988.

◎ Yamashita H, ten Dijke P, Huylebroeck D, Sampath TK, Andries M, Smith JC, Heldin C-H, and **Miyazono K**. (1995) Osteogenic protein-1 binds to activin type II receptors and induces certain activin-like effects. ***J Cell Biol.*** 130, 217-226.

◎ Rosenzweig BL, Imamura T, Okadome T, Cox GN, Yamashita H, ten Dijke P, Heldin C-H, and **Miyazono K**. (1995) Cloning and characterization of a human type II receptor for bone morphogenetic proteins. ***Proc Natl Acad Sci USA.*** 92, 7632-7636.

◎ Ichijo H, Nishida E, Irie K, ten Dijke P, Saitoh M, Moriguchi T, Takagi M, Matsumoto K, **Miyazono K**, and Gotoh Y. (1997) Induction of apoptosis by ASK1, a mammalian MAPKKK that activates SAPK/JNK and p38 signaling pathways. ***Science.*** 275, 90-94.

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◎ Akiyoshi S, Inoue H, Hanai J-i, Kusanagi K, Nemoto N, **Miyazono K,** and Kawabata M. (1999) c-Ski acts as a transcriptional co-repressor in TGF-β signaling through interaction with Smads. ***J Biol Chem.*** 274, 35269-35277.

◎ Watabe T, Nishihara A, Mishima K, Yamashita J, Shimizu K, Miyazawa K, Nishikawa S, and **Miyazono K**. (2003) TGF-β receptor kinase inhibitor enhances growth and integrity of embryonic stem cell-derived endothelial cells. ***J Cell Biol.*** 163, 1303-1311.

◎ Koinuma D, Shinozaki M, Komuro A, Goto K, Saitoh M, Hanyu A, Ebina M, Nukiwa T, Miyazawa K, Imamura T, and **Miyazono K**. (2003) Arkadia amplifies TGF-β superfamily signalling through degradation of Smad7. ***EMBO J.*** 22, 6458-6470.

◎ Maeda S, Hayashi M, Komiya S, Imamura T, and **Miyazono K**. (2004) Endogenous TGF-β signaling suppresses maturation of osteoblastic mesenchymal cells. ***EMBO J.*** 23, 552-563.

◎ Kano MR, Bae Y, Iwata C, Morishita Y, Yashiro M, Oka M, Fujii T, Komuro A, Kiyono K, Kaminishi M, Hirakawa K, Ouchi Y, Nishiyama N, Kataoka K, and **Miyazono K**. (2007) Improvement of cancer-targeting therapy using nanocarriers for intractable solid tumors by inhibition of TGF-β signalling. ***Proc Natl Acad Sci USA.*** 104, 3460-3465.

◎ Komuro A, Yashiro M, Iwata C, Morishita Y, Johansson E, Matsumoto Y, Watanabe A, Aburatani H, Miyoshi H, Kiyono K, Shirai Y, Suzuki HI, Hirakawa K, Kano MR, and **Miyazono K**. (2009) Diffuse-type gastric carcinoma: Progression, angiogenesis, and transforming growth factor-β signaling. ***J Natl Cancer Inst.*** 101, 592-604.

◎ Suzuki HI, Yamagata K, Sugimoto K, Iwamoto T, Kato S, and **Miyazono K**. (2009) Modulation of microRNA processing by p53. ***Nature.*** 460, 529-533.

◎ Ikushima, H., Todo, T., Ino, Y., Takahashi, M., Miyazawa, K., and **Miyazono, K.** (2009) Autocrine TGF-β signaling maintains tumorigenicity of glioma-initiating cells through Sry-related HMG-box factors. ***Cell Stem Cell.*** 5, 504-514.

◎ Suzuki HI, Arase M, Matsuyama H, Choi YL, Ueno T, Mano H, Sugimoto K, and **Miyazono K**. (2011) MCPIP1 ribonuclease antagonizes dicer and terminates microRNA biogenesis through precursor microRNA degradation. ***Mol Cell.*** 44, 424-436.

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TGF-β Signaling in Regulation of Cancer

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TGF-β elicits both tumor promotive and suppressive functions during progression of cancer. We present our recent findings on TGF-β family signaling in progression of cancer, focusing on induction of epithelial-mesenchymal transition (EMT) by TGF-β. TGF-β induces EMT through activation of Smad and non-Smad signaling pathways. Upon induction of EMT in cancer cells, TGF-β enhances cell motility and degrades extracellular matrices, leading to invasion and metastasis of cancer. Inhibition of TGF-β signaling by Smad7 or small molecular weight TGF-β inhibitor(s) results in prevention of cancer metastasis in mouse models. Multiple transcription factors, including δEF1/ZEB1, SIP1/ZEB2, Snail, and Slug, play critical roles in TGF-β-induced EMT.

Thyroid transcription factor-1 (TTF-1/Nkx2-1) is expressed in lung cancer, but its functional roles remain to be elucidated. We have found a novel function of TTF-1 that inhibits TGF-β-mediated EMT and restores epithelial phenotype in lung adenocarcinoma cells. This effect was accompanied by down-regulation of TGF-β target genes, including Snail and Slug. We have further studied the mechanism through which TTF-1 inhibits the functions of TGF-β and found that TTF-1 disrupted the Smad3/Smad4 complex in the nucleus. Genome-wide analyses by ChIP-seq revealed that TTF-1 co-localized with Smad3 on the chromatin and altered the binding patterns of Smad3 throughout the genome. Our findings provide a new model of regulation of TGF-β-Smad signaling. Moreover, analyses using next generation sequencers allowed us to identify new target genes of TGF-β and TTF-1, which appeared to be involved in cancer cell metabolism and cell growth and survival through cross-talk with other signaling pathways.

NOTE :

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Session II

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Selected publications: (2009~)

◎ **Lin CH**, Shih CH, Tseng CC, Bien MY, and Chen BC*. (2014) CXCL12 induces connective tissue growth factor expression in human lung fibroblasts through the Rac1/ERK/AP-1 pathway. ***PLoS One.*** 9:e104746. dio:10.1371/journal.pone.0104746.

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Connective Tissue Growth Factor (CTGF) Mediates Fibrocyte Differentiation in Chronic Obstructive Asthma

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Bronchial asthma is characterized by persistent airway inflammation and structural remodeling of the airways. There are several clinical pathophysiologic characteristics of airway remodeling in patients with asthma, including epithelial detachment, increased smooth muscle mass, goblet cell hyperplasia, and subepithelial fibrosis formation. Increasing lines of evidence have shown that fibrocytes, bone marrow–derived progenitor cells that express CD34, CD45, and collagen I (Col-I), have been implicated in the pathogenesis of pulmonary fibrosis and airway remodeling. Fibrocytes possess increased differentiability into α-smooth muscle actin $(\alpha\text{-SMA})^+$ myofibroblasts in chronic obstructive asthma (COA) and contribute to pulmonary fibrosis. Endothelin-1 (ET-1) induces matrix-associated gene expression through the ET_A receptor (ET_AR) and promotes fibroblast differentiation. However, the mechanism of fibrocyte differentiation remains unclear. We investigate that the roles of the ET_AR and connective tissue growth factor (CTGF) expression in fibrocytes in the development of fibrosis in COA. Blood nonadherent non-T (NANT) cells were isolated, and fibrocytes expressing CD45, collagen I, CTGF, ET_AR, or α-SMA were identified by flow cytometry. We showed the accumulation of fibrocytes in bronchial walls and overexpression of CTGF in fibrocytes from patients with COA. After being cultured, CTGF was increased in fibrocytes from patients with COA, but not from those of normal participants or patients with asthma without obstruction. Serum levels of ET-1 and the expression of the ET_AR in fibrocytes were significantly higher in patients with COA compared with normal participants and patients with asthma without obstruction. Treatment with the ET_AR antagonist (BQ123), but not ET_BR antagonist (BQ788), reduced the expression of CTGF and α-SMA in fibrocytes and fibrocyte differentiation in patients with COA. Furthermore, treatment with BQ123 or an anti-CTGF antibody attenuated α-SMA expression induced by ET-1 in fibrocytes from normal participants. Our findings demonstrate for the first time that the ET_AR pathway is vital for CTGF expression, which results in fibrocyte differentiation in COA, and suggests that an ET_AR antagonist may be a potential antifibrotic agent in preventing the development of fibrosis in patients with COA.

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Recent Selected Publications:

◎ Chou JL, Huang RL, Jacqueline Shay, Chen LY, Lin SJ, Pearlly S. Yan, Chao WT, Lai YH, Lai YL, Chao TK, Lee CI, Tai CK, Wu SF, Kenneth P. Nephew, Tim H.-M. Huang, **Lai HC*** and Michael W.Y. CHAN* Hypermethylation of the TGF-beta target, ABCA1 is associated with poor prognosis in ovarian cancer patients. ***Clinical Epigenetics.*** 2014 (in press)

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DNA Methylation Development of Biomarkers in GYN Cancers: Translating Research to Clinical Practice

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Epigenetic changes play an important role in development. Cancer is a developmental disorder. Epigenetic alterations have been shown to occur in many types of cancers, including the gynecology cancers. Epigenetics defined as a heritable change in gene expression without alteration of the DNA sequence itself which including DNA methylation, histone modification, nucleosome reposition, and posttranscriptional gene regulation by micro-RNAs. The most studied epigenetic alteration is DNA methylation. Cancer genomes are globally hypomethylated and hypermethylated at specific sequences such as promoter or enhancer regions compared to normal. As epigenetic silencing of tumor suppressor genes by promoter hypermethylation is commonly observed in human cancers. Changes of DNA methylation could serve as potential biomarkers for cancer screening and as a means of appraising the prognosis of cancer patients.

We have been devoting to the discovery and translation of DNA methylation biomarkers in gynecological cancer for 10 years. The discovery, erification, validation and in vitro diagnostics manufacturing have made the clinical application of PAX1 methylation for cervical cancer detection possible this year. We further explored the methylation biomarkers for ovarian and endometrial cancer detection. The preliminary results are promising.

The development of DNA methylation biomarker may change the way of GYN cancer screening in the near future.

NOTE :

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Recent Selected Publications: *Corresponding author

◎ Chang TS, Wu YC, Su WC, Chi CC, Chang PJ, Lee KF, Liu JJ, Tung SY, Kuo LM, Ho HN, Ling TY, and **Huang YH***. (2014) Activation of IL6/IGF-IR confers poor prognosis of HBV-related hepatocellular carcinoma through induction of OCT4/NANOG expression. ***Clin Cancer Res.*** In Press

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◎ **Huang YH***, Cheng CC, Ho HN, Chou CK, Shen CN, Kuo HC, Wu, TJ, Wu YC, Hung YC, Chang CC and Ling TY.(2009) Pluripotency of mouse spermatogonial stem cells maintained by IGF-1 dependent signaling pathway. ***FASEB J.*** 23: 2076-2087.

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Homeostasis of Pluripotent Transcription Factor OCT4 in Stem Cells and Cancer

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The expression levels of pluripotency-related genes in cells, like pluripotent transcription factor OCT4, are linked to drug susceptibility which challenges the current cancer therapy. Niche environment apparently plays a critical role in cell stemness regulation either of somatic- or embryonic stage. In this talk, two human diseases of somatic hepatocellular carcinomas (HCC) and embryonic pluripotent germ cell tumors seminoma and embryonic carcinoma will be discussed to address the potential homeostasis mechanism of pluripotent transcription factor OCT4 in stem cells and cancer, and its implication of the drug susceptibility and poor prognosis in cancer therapy.

Hepatocellular carcinoma (HCC) is an inflammation-associated cancer which is commonly associated with chronic virus infection. In a large cohort of frozen HCC samples, we found the niche inflammatory cytokine IL-6 is critical for the re-expression of OCT4 in patient tissues. The underlying mechanism involves that IL-6-induced IGF/IGF-IR signal activation particularly for hepatitis B virus (HBV)-related HCC (HBV-HCC), and is associated with tumor aggressiveness and recurrence. Niche IL-6 stimulated the expression of autocrine IGF-I and IGF-IR in a STAT-dependent manner, which stimulated the stemness-related properties in both the cell lines and the xenograft mouse tumors. The inhibition of the IGF-IR activation by RNA interference and molecular inhibitor significantly suppressed the IL-6-induced stemness-related properties in vitro and in vivo. These findings suggest that the IL-6-induced IGF-IR signaling is a potential strategy targeting on cancer stemness for individualized adjuvant therapy against HBV-HCC.

Human seminoma and embryonal carcinoma (EC) are cancer stem cells transformed from the embryonic pluripotent primordial germ cells. This human disease provides an excellent cell model to study the OCT4 homeostasis as the tumor express high OCT4 levels in cells. We found niche hypoxia is able to down-regulate the OCT4 level and results in chemoresistance and poor prognosis by regulating the SUMO1 peptidase SENP1. Overexpression of SENP1 reduced the Su-OCT4 level induced by SUMO1gg overexpression, thereby maintaining OCT4 levels and enhancing chemosensitivity. Mechanistic investigations revealed that OCT4 sumoylation occurred at K123, as overexpression of an OCT4-K123R mutant effectively reduced the level of Su-OCT4 under hypoxic conditions. These results demonstrated that hypoxia reduces OCT4 expression levels in pluripotent germ cell tumors to increase drug resistance, and these effects could be countered to ablate the suppressive effects of hypoxia on chemosensitivity.

NOTE :

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◎ Lin YC, Huang DY, Chu CL, Lin YL, **Lin WW**.(2013) The tyrosine kinase Syk differentially regulates Toll-like receptor signaling downstream of the adaptor molecules TRAF6 and TRAF3. ***Science Signaling.*** 6:ra71.

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Energy Homeostasis and Mitochondrial Signals in Cancer Cells Under Nutrient Starvation

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Hypoxia was shown to induce hypoxia-inducible factor (HIF)-1α expression which supports many cellular changes required for tumor growth and metastasis. In addition to hypoxia, nutrient deprivation is another stress condition widely existing in solid tumors due to the poor blood supply, but the effect on cancer cell metabolism is not yet clear. Our data showed that nutrient deprivation induces ROS/AMPK-dependent activation of PDK which inhibited PDH activity, and then enhanced Warburg effect. On the other hand, nutrient deprivation enhanced HIF-1α mRNA binding to ribosome which induced HIF-1α expression through ROS/AMPK signaling. Rather we found it occurred through cap-independent but internal ribosome entry site (IRES)-dependent translation. Interestingly, inhibition of autophagy by si-ATG5, 3-methyladenine, and chloroquine, but not si-Beclin-1, significantly reversed nutrient deprivation-induced HIF-1α responses. However, different from nutrient starvation, si-Beclin 1, but not si-ATG5, inhibited hypoxia-induced HIF-1α protein expression. We also noticed that interfering mitochondria activity by FCCP or rotenone can significantly reversed nutrient deprivation-induced HIF-1α expression. This indicated the important role of mitochondria in manipulating nutrient deprivation-induced HIF-1α expression. Taken together, we highlight a link from alternative autophagy to cap-independent protein translation of HIF-1α under two unique stress conditions. We demonstrated that Beclin 1-independent autophagy is involved in the positive regulation of nutrient deprivation-induced HIF-1α IRES activity and protein expression, while ATG5-independent autophagy is involved in HIF-1α protein expression caused by hypoxia.

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Recent Selected Publications:

◎ Yang IH, Chang JM, Wong JH, Chen BK, Hsu WL, **Chang WC.** Involvement of intracellular calcium mobilization in IL-8 activation in human retinal pigment epithelial cells. ***Investigative Ophthalmology & Visual Science.*** 2015, in press.

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Toward High Precision Cancer Medicine: Lessons Learned

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Tumor metastasis is the major cause of death among cancer patients, with >90% of cancer-related death attributable to the spreading of metastatic cells to secondary organs. Store-operated Ca^{2+} entry (SOCE) is the predominant Ca^{2+} entry mechanism in most cancer cells, and stromal interaction molecule 1 (STIM1) is the endoplasmic reticulum (ER) Ca^{2+} sensor for store-operated channels. Here we reported that the STIM1 was overexpressed in colorectal cancer (CRC) patients. STIM1 overexpression in CRC was significantly associated with tumor size, depth of invasion, lymph node metastasis status and serum levels of carcinoembryonic antigen. Furthermore, ectopic expression of STIM1 promoted CRC cell motility, while depletion of STIM1 with short hairpin RNA inhibited CRC cell migration. Our data further suggested that STIM1 promoted CRC cell migration through increasing the expression of cyclooxygenase-2 (COX-2) and production of prostaglandin E2 (PGE2). Importantly, ectopically expressed COX-2 or exogenous PGE2 were able to rescue migration defect in STIM1 knockdown CRC cells, and inhibition of COX-2 with ibuprofen and indomethacin abrogated STIM1-mediated CRC cell motility. In short, our data provided clinicopathological significance for STIM1 and SOCE in CRC progression, and implicated a role for COX-2 in STIM1-mediated CRC metastasis. Our studies also suggested a new approach to inhibit STIM1-mediated metastasis with COX-2 inhibitors.

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◎ Chen CA, Chen SY, Wang JK, Tseng WY, **Chiu HH**, Chang CI, Chiu IS, Chen YS, Yang MC, Lu CW, Lin MT, Wu MH. (2014) Ventricular geometric characteristics and functional benefit of mild right ventricular outflow tract obstruction in patients with significant pulmonary regurgitation after repair of tetralogy of Fallot. ***Am Heart J***. 167:555-561.

TGF beta and Angiotensin Networking in Vascular Remodeling and Potential Therapeutic Targets in Marfan Syndrome

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Aortic aneurysms and dissection develop as a result of maladaptive remodeling of the vascular extracellular matrix, which are the main life-threatening consequences of Marfan syndrome. Marfan syndrome, an autosomal dominant hereditary disorder of connective tissue, is caused by fibrillin-1 gene mutation. Fibrillin-1 is the major component of elastin-associated microfibrils found throughout the extracellular matrix of the aortic media. Angiotensin II and TGF-ß have been showed to play important roles in cardiovascular remodeling. Recent evidences support that Fibrillin-1 regulates TGF-β activation by sequestering it in association with specific latent TGF-β binding proteins. Loss of fibrillin-1 may then lead to over-release of TGF-β, which induces activation and overexpression of Smad-dependent profibrotic signaling pathway and ERK 1/2-mediated increased synthesis of matrix metalloproteinases, proteoglycan production, collagen gene expression and extracellular matrix degeneration. Hence, the TGF-β antagonism represented a productive treatment strategy in Marfan syndrome.

NOTE :

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Recent Selected Publications:

◎ Wu HH, **Cheng YW**, Cheng Tsai J, Wu TC, Chen CY, and Lee H. (2010) Subcellular localization of apurinic endonuclease 1 promotes lung tumor aggressiveness via NF-κB activation. ***Oncogene.*** 29(30):4330-4340.

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◎ Ke TW, Wei PL, Yeh KT, Chen WTL, **Cheng YW***. (2014) MiR-92a Promotes Cell Metastasis of Colorectal Cancer through PTEN mediated PI3K/AKT pathway. ***Ann Surg Oncol.*** accepted.

Role of HPV in Lung Cancer: Pathogenesis and Therapeutic Effect

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Lung cancer is leading cause of cancer death in Taiwanese women who are mostly to be life-time never smokers. Majority of drugs and combinations are used to treat with smoking lung cancer patients, not for nonsmokers. However, the 5-year survival rate in lung cancer patients remains ~15% during the past three decades. Therefore, dissolving tumor recurrence and drug resistance is urgently needed for improving outcome in lung cancer, especially in nonsmokers. Our previous study indicated that human papillomavirus (HPV) oncogenic subtypes 16/18, which are involved in cervical cancer, may also be involved in the pathogenesis of lung cancer among Taiwanese women. Therefore, we suggested that HPV infection could contribute to tumor recurrence and drug resistance via an E6 oncoprotein expression. In our studies, we demonstrated that HPV involved in lung tumorigenesis is partially mediated through (1) p53 inactivation, (2) up-regulation of IL-6, Mcl-1, hTERT, and expressions, (3) reduced p21 via alteration of p53/DDX3 pathway, and (4) TIMP-3 inactivation. In addition, we also found that HPV involved in clinical outcome and therapeutic response of lung cancer patients is partially mediated through (1) Paxillin overexpression by E6 via reduced miR-218 expression,(2) p21 synergistically suppressed by E6 via DDX3/p53 pathway, (3) loss of DDX3 by p53 inactivation via MDM2/Slug/E-cadherin pathway, (4) loss of TIMP-3 induced IL-6 production via the tumor necrosis factor α/nuclear factor κB signaling, and (5) reduced XRCC3 and XRCC5 gene expression by E6 via induced promoter hypermethylation. Thus, we suggested that selecting feasible molecular targeting drugs may be more effective in HPV-infected lung cancer therapy.

NOTE :

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